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"Follow-on" Biologic Competition in the Biopharmaceutical Marketplace

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Objective: To describe the implications of a follow-on biologic approval process with focus on current stakeholders, implications of the status quo, and recommendations for future policy.

Data Sources: A search using MEDLINE, International Pharmaceutical Abstracts, MedAdNews, FDC-Pink Sheets, and Google index directories was conducted with terms such as biologic, biopharmaceutical, generic, and follow-on.

Study Selection: Articles pertaining to the follow-on biologic debate were considered by the authors for study inclusion.

Data Extraction: Not applicable

Data Synthesis: Over the past decade, the biopharmaceutical market has experienced significant growth in the number of product approvals and sales. In contrast to prescription medications, biologic agents currently lack an abbreviated regulatory approval process. Evidence from the Drug Price Competition and Patent Restoration Act suggests that reducing barriers to generic competition in the pharmaceutical market successfully increases generic market penetration and reduces overall prices to consumers. Although there are scientific and regulatory dissimilarities between biopharmaceuticals and other medications, a follow-on biologic approval process has the potential to play an important role in containing growth in pharmaceutical spending. In addition to biopharmaceutical and generic biopharmaceutical manufacturers, stakeholders with a vested interest in this debate include individual consumers who continue to bear the burden of spending increases in the pharmaceutical market.

Conclusion: The debate over a follow-on process likely will be difficult as parties seek a balance between incentives for research and discovery of new biopharmaceutical agents and consumer benefits and safety.

Introduction

The biopharmaceutical industry emerged in 1982 with the development and market approval of recombinant human insulin (Humulin – Eli Lilly). Since that time, the industry has led major advancements in the management and prevention of previously untreatable disease through the design of innovative compounds. Two examples include thrombolytics for the treatment of acute myocardial infarction and recombinant erythropoietin for management of anemia during end-stage renal disease. Both products yielded significant improvements over previously available therapeutic alternatives for each condition. Consequently, the biotechnology industry has experienced growth in the annual number of new products and indications approved.[1] (See Figure 1)

Sales of biopharmaceuticals also have grown rapidly. Table one shows the growth in sales for 35 biopharmaceuticals among the world's 200 best selling medications in 2003.[2] Overall these select biologics accounted for approximately $35 billion in global sales in 2003. It is estimated that the North American market accounts for approximately 60% of global biotechnology sales.[3] This corresponds to approximately $21 billion in sales in the North American market alone. Furthermore, sales of these top selling biopharmaceuticals have grown 94% from 2000 to 2003. This represents an average annual increase in sales of 25% over this time period.

At the same time, national growth in spending for all prescription drugs, including biologics, has intensified. Prescription expenditures experienced a 15.3% increase over the previous year, once again exceeding the 9.3% rise in total health expenditures for 2002.[4] This double digit expansion has outpaced other sectors of health care spending. As a result, prescription medications have become a central issue in explaining the sustained growth in U.S.

health care expenditures. The rapid expansion of the biopharmaceutical market has led to scientific, regulatory and economic debate on how to maintain an environment that provides access to affordable biopharmaceuticals and creates incentives for continued innovation and competition in the biotechnology market.

Recently, patent expiration and loss of market exclusivity on several of the earliest biopharmaceuticals stimulated a discussion on the role of generic or "follow-on" biologics in the biotechnology market. At present, the U.S. pharmaceutical regulatory process does not have a well-defined pathway for the approval of follow-on biologics. Due to the growing amount of resources devoted to biopharmaceuticals, decisions surrounding the future of generic competition in the biotechnology market will require consensus on the best technique to maximize the well-being and safety of society while maintaining a vital biotech industry.

In this paper, we first review the history of generic medication policy in the U.S. with emphasis on the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act). Next, we examine the regulatory oversight of biotechnology products and review the legislative actions responsible for the current differences between drugs and biologics. We also discuss the existing approval process for follow-on biologics in the U.S. Finally, we consider the implications of follow-on biologics in the health care delivery system with focus on the current stakeholders, implications of the status quo and some recommendations to guide future pharmaceutical policy for biologics.

The scientific literature and independent media have relied on an assortment of terms for describing medications, both biologics and non-biologics. For the remainder of this paper, we will use the term *biologic* or *biopharmaceutical* to indicate a branded, innovative, or single-source biologic product. We will use the term *follow-on biologic* to specify a generic version of

a branded biologic medication. The term generic biologic is generally considered inappropriate because it implies an exact copy of the originator's product, which currently is impossible due to limitations in technology.[5] Finally, when the term *drug* or *generic* is used, it refers to a "small-molecule" medication or a product that is chemically derived.

History of Generic Medication Policy

Researchers estimated the total cost of bringing a new molecular entity (NME) to market in the U.S. averaged $802 million dollars in 2000 when the cost of capital and company drug failures are capitalized.[6] The accuracy of this estimate has become controversial but general consensus regards the pharmaceutical discovery and development process as a perilous undertaking fraught with uncertainty.[7] Due to the expense of creating and developing novel pharmaceutical products, the U.S. government relies on intellectual property rights through provision of patents to protect innovative products from competition for a period of time. This safeguard provides the patent holder a temporary monopoly to recoup the costs of research and development and earn sufficient profits to encourage continued innovation in the marketplace. After patent expiration, generic producers may copy the innovator product, enter the market, and generate price competition among several competing firms. Generic entry has played an important role within the U.S. pharmaceutical market, with generic medications costing consumers significantly less than single source brand products.[8] Understanding the significance of competition between brand and generics begins with an examination of the historic regulatory amendments and market influences that brought us to the present day.

In 1962, the Food Drug and Cosmetic Act (FDCA) was modified by passage of the Keafauver-Harris Amendment.[9] Among other things, this amendment required pharmaceutical companies to provide evidence of both safety and efficacy for new medications before gaining

market approval. In addition, this legislation mandated generic pharmaceutical producers to conform to the same requirements as the innovator before market entry. This regulatory change prohibited generic producers from relying on previous data generated by the innovator due to its designation as a trade-secret. As a result, this legislation created a significant barrier-to-entry for producers of generic medications.

Grabowski and Vernon analyzed the impacts of this policy through evaluation of pharmaceutical innovation and competition during the post-1962 regulatory environment.[10] The authors examined data on the top 200 drugs of 1983 and found that 62% of medications with expired patents had not experienced generic competition, including two top twenty medications with combined sales of over $200 million (1983 dollars). The authors also examined the rate of generic competition for antibiotics and all drugs approved prior to 1962. Companies producing generics of these drugs were permitted to rely on previously published evidence of safety to gain market entry. Comparatively, the authors reported that more than 90% of these off-patent medications had generic competition. Grabowski and Vernon concluded that regulatory changes in 1962 had indeed created a significant barrier for pharmaceutical innovation and competition and resulted in sluggish generic penetration for off-patent medications after 1962.

The U.S. Congress took notice of the adverse market conditions in the pharmaceutical industry and began discussing possible legislative solutions. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) and it was signed into law by President Reagan. This legislation had two purposes.[11] First, it lessened the current barriers to market entry for generic products (Title I). Second, it created provisions for the pharmaceutical industry to regain patent protection for time lost in clinical development and

regulatory review (Title II). Thus, this legislation created a compromise between brand and generic producers of pharmaceuticals.

In order to stimulate generic market entry, the Hatch-Waxman Act amended the requirement for generic manufacturers to reproduce both safety and efficacy data of the innovator drug before gaining market approval. The law created an Abbreviated New Drug Application (ANDA) under section 505(j) of the FDCA, which limited generic market approval requirements to demonstration of "bioequivalence" and prohibited the FDA from requiring additional information.[11] One of four certifications must be made when submitting an ANDA to the FDA. The following explanations are attached to each certification: 1) the drug for which the ANDA has been submitted is not patented; 2) the product patent already has expired; 3) the date the patent will expire with projected generic entry after that date; and 4) the current product patent is not infringed or is invalid.[11] The Hatch-Waxman Act also provides a period of "180-day market exclusivity" for the first generic producer to gain market approval through a paragraph IV filing.[12] This process created a strong financial incentive for generic producers to challenge patents it believed were invalid, unenforceable, or not infringed.[13] As a result, generic companies could then pursue market entry earlier in the drug product life cycle.

In addition to the ANDA outlined in section 505(j), an alternative mechanism was created to allow the sponsor of a New Drug Application (NDA) to gain market approval. This pathway is outlined in section 505(b)(2) of the FDCA and allows a company to rely on previously published data or prior FDA rulings on the safety and efficacy of a product to gain market approval. Typically, this route is utilized when a product is not identical to the innovator and cannot be considered a generic or when additional clinical testing is required to gain market approval.

As a compromise, Title II of the Hatch-Waxman Act offered innovator pharmaceutical firms the ability to recoup patent life lost during clinical development and regulatory oversight. The formula used to calculate the amount of patent life regained is equal to the sum of all of the time spent during FDA review (i.e., approval time for a NDA) plus one-half of the time spent in clinical testing.[14] This determination is subject to a variety of restrictions and limits including a maximum extension of 5 years and a limit of 14 years on total effective patent life. Also, the legislation provided an initial period of market exclusivity equal to 5 years during which time no ANDAs could be filed.

Despite some criticisms of this legislation, it was largely successful at achieving its initial aims. Empirical evidence of pharmaceutical market adjustments after enactment of Hatch-Waxman was published in 1996.[15] Including data collected during an earlier analysis[16], the authors assembled information on 22 medications experiencing generic competition for the first time between 1989 and 1993. Using information on average sales price for the brand and generic products, the authors compared trends in generic competition and utilization to similar measures in the pre Hatch-Waxman era (described above). On average, generic products entered the market at substantially reduced prices and experienced increasing market share during this period. Thus, these findings implied that the legislation had been effective at fostering generic entry and price competition.

Evaluation of the Hatch-Waxman act on pharmaceutical innovation has proved more difficult to assess. However, the legislation was successful at increasing the average effective patent life for new molecular entities by more than 2 years, thereby increasing an innovator firm's total return on investment.[16] In addition, R&D spending levels as a percentage of brand-name manufacturers' sales revenue grew 5 percentage points between 1983 and 1995.[17] During

this same period, brand-name manufacturers' sales revenues more than tripled. At a minimum, it would appear the incentive to invest in the development of new pharmaceutical products remained intact after the enactment of Hatch-Waxman Act.

Regulatory Oversight of Biopharmaceutical Products

The most important distinctions between biologics and drugs can be classified as either regulatory or scientific. From a regulatory perspective, biologics are governed by the Public Health Service Act (PHSA) which provides the following statutory definition of what constitutes a biologic: "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivative, allergenic product, or analogous product, or arsphanamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of disease or condition of human beings".[18] In comparison, a drug as stipulated by the Food Drug and Cosmetic Act (FDCA) can be defined as "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" or "articles (other than food) intended to affect the structure of any function of the body".[19] Based on these broad definitions, many biologics could potentially be categorized as drugs. However, biologics and drugs undergo different sets of regulatory oversight, due to both historical differences in product handling and unique physical characteristics that arise when describing biologics (discussed below in greater detail).

The scientific and technical dissimilarities between biologics and drugs are considered the primary reason for relying on different legislation to manage the U.S. regulatory environment. In an article by David Korn[20], the differences were described as follows: (1) biologics (as the name suggests) have a biologic origin or are remarkably similar to actual biologic compounds (e.g. proteins or enzymes); (2) biologics are almost exclusively given via injection compared to drugs which are most commonly taken orally; (3) biologics often are much

larger molecules than drugs; (4) biologics tend to be more heterogeneous than drugs and as such, more difficult to model or characterize; (5) biologics tend to be more dependent on the manufacturing process than drugs; and (6) biologics have a higher risk of immune related adverse reactions than synthetic drugs.

In contrast to other medications that obtain market approval through filing of an NDA, biologics are approved through a Biologic License Application (BLA) demonstrating that the product is safe, pure, and potent. In actual practice, the requirements for gaining market approval for a new or innovative biologic are very similar to novel non-biologic drugs.[21] Until recently, the regulatory reviews for biologics and small-molecule drugs were supervised by separate divisions at the Food and Drug Administration (FDA). Biologics were evaluated by the Center for Biologic Evaluation and Research (CBER) and small-molecule drugs (including ANDAs) were reviewed by the Center for Drug Evaluation and Research (CDER). As of June 30, 2003, the responsibility of regulating several types of biologics including monoclonal antibodies, proteins, immunomodulators, and growth factors shifted to the CDER.[22] This restructuring will consolidate the process of approving new medications (whether biologically or chemically derived) and may allow for a smother transition to a regulatory environment that includes a well-defined pathway for follow-on biologics.

U.S. Approval Process for Follow-On Biologics

Due to the aforementioned regulatory and scientific differences, the U.S. does not currently have an abbreviated application process in place for the approval of follow-on biologics. In 1984, few biotechnology products were commercially available and biologics did not consume the level of resources observed currently. As a result, the legislation was limited to amending the FDCA and did not alter the PHSA. This left the market for biologics untouched.

Under current law potential generic competitors are forced to conduct and finance complete clinical testing (analogous to the innovator) in order to gain market approval. As existing patents for biologics reach expiration, this requirement will substantially raise follow-on entry costs and result in higher product prices.

An interesting caveat exists due to the historic handling of some biologics. Several of the earliest biologics were approved and regulated under the FDCA instead of the PHSA (e.g., human growth hormones and insulin). Hence, people have speculated that these products would be open for generic competition via the 505(b)(2) abbreviated pathway discussed above. In fact, recent congressional testimony by FDA Commissioner Lester Crawford supported this position.[23] On June 23rd, 2004 Commissioner Crawford stated "From a legal perspective, for products approved under section 505 of the FDCA, we also believe there is existing authority to allow applications for such products under section 505(b)(2) of the FDCA, relying on the earlier approval of the innovator product." He goes on to point out that the agency does "not believe such authority exists for follow-on biologics application under section 351 of the PHSA that relies on the prior approval of the biological product or on data submitted by another sponsor."

With this principle in mind, Omnitrope-Sandoz has submitted an NDA under the 505(b)(2) process for human somatrope, a follow-on version of Pfizer's Genotropin.[24] The FDA decision on this application may set an important precedent for handling the approval of future follow-on biologics governed under the FDCA. However, the FDA has deferred decision on approval of the abbreviated follow-on application citing uncertainty with scientific and regulatory issues.[25] Regardless of the outcome, the regulatory pathway for follow-on biologics will continue to garner a great deal of attention because the majority of biologics are governed

under the PHSA and as such are not eligible for approval under the 505(b)(2) pathway included in the FDCA.

More follow-on biologic filings are likely in the near future as older biopharmaceuticals lose patent protection. For example, 12 biologics in Table 1 originally were approved before 1993. These agents are of particular interest because they have been approved for at least 12 years and would be the most likely candidates for follow-on competition. Further analysis shows that these products accounted for approximately $14 billion or 40% of biopharmaceutical sales in 2003. Generic companies are eager to transition into this market while branded biotech companies are reluctant to allow competition due to the likely revenue losses that would occur without continued patent protection. As a result, generic entry in the biotechnology industry has become a sensitive regulatory problem.

Implications of Follow-On Biologics in the Health Care Delivery System

Evolving follow-on biologic regulations will impact numerous segments of the pharmaceutical marketplace. At a minimum, stakeholders include consumers, the U.S. government, insurance providers, corporate producers of brand biotechnology products, generic manufacturers and healthcare providers. The needs of consumers hold a prominent position in the follow-on biologic debate. Recent trends suggest that while reliance on biologic products continues to increase, consumers are paying higher premiums for health insurance and are responsible for paying a larger portion of the price of these products.[26] Although consumers are affected significantly by lack of follow-on competition, oftentimes they are reliant upon third parties to make appropriate decisions upon their behalf. This is partly attributable to asymmetry of information between consumers, physicians, and insurers. Significant progress in establishing

a follow-on biologic procedure is unlikely until consumers take on a prominent position in the debate.

The U.S. government has several roles that warrant consideration. First, the government has an imperative to craft an effective health policy. Historically, pharmaceutical market inefficiencies have been viewed as harmful to the public interest, requiring government intervention. Second, the U.S. government plays a large role in purchasing biologics for patient treatment through public insurance programs. For instance, Medicare is the largest purchaser of erythropoietin in the U.S. Spending on this product alone accounted for $1.1 billion or 13% of the total expenditures for drugs covered under Medicare Part B in 2002.[27] The expansion of Medicare to include coverage of outpatient prescription drugs will increase the importance of effective regulatory policy that provides affordable access to pharmaceuticals.[28]

Private insurance companies are likely to be involved in the decision-making process as the debate on regulatory reform for biologics develops. Insurance companies continue to pay for an increasing proportion of total drug expenditures.[29] This has led third party providers to adopt a variety of tactics to control pharmaceutical spending including attempts to increase patient utilization of generic medications. Financial incentives to encourage generic use have been successful at eroding brand-name market share immediately after generic entry. A recent example of this phenomenon followed the patent expiration of fluoxetine (Prozac-Eli Lilly) in August of 2001. Data from the largest U.S. pharmacy benefit manager showed that after only two weeks, the number of prescriptions for generic fluoxetine exceeded the brand.[30] This adoption rate was much faster than previous reports and demonstrated the potential of insurance driven generic utilization.

Branded biotechnology companies are another stakeholder in this debate. They have argued that it would be extremely difficult to create an abbreviated generic biologic approval system. The Biotechnology Industry Organization (BIO) has been one of the most vocal critics of follow-on biologics. In April 2003, BIO submitted a Citizen Petition to the FDA indicating its stance on follow-on therapeutic proteins and asked the agency do the following: "(1) conduct a meaningful public participation process on the agency's policies on the issue of follow-on approval; (2) refrain from approving any application for a therapeutic protein product that does not contain a full complement of original non-clinical and clinical data and that relies on information contained in another applicant's application; (3) refrain from preparing, publishing, circulating or issuing any new guidance for industry concerning follow-on therapeutic proteins; and (4) withdraw its 1999 Draft Guidance for Industry: Applications Covered by Section 505(b)(2)".[31] Similar petitions have been filed with the FDA by individual pharmaceutical companies aimed at halting the approval of any biologic by the 505(b)(2) pathway. Branded biotechnology companies believe an abbreviated process for follow-on biologics would violate an innovator's intellectual property rights and create additional patient safety concerns due to the lack of complete clinical testing.

Conversely, generic manufacturers believe it is possible to create a system capable of producing safe and effective generic biologics without mandating a full review process (complete preclinical and clinical testing). The Generic Pharmaceutical Association (GPhA) favors an approved follow-on biologic pathway. GPhA has accused the Pharmaceutical Research and Manufacturers of America (PhRMA) and BIO of "dragging their feet" in allowing follow-on competition in biologics and harming millions of American consumers in the process.[32] Generic manufacturers admit that a system of "bioequivalence" analogous to the

ANDA process for chemical drugs is not the right answer in light of current technological capabilities. However, they also maintain that a full battery of clinical testing is repetitive and unnecessary.

Finally, providers of health care services will likely influence the formation and implementation of new regulatory policy for biologics. Physicians are prominent because they are the primary prescribers of prescription medications, including biologics. In addition, physicians wield significant influence over patient opinions regarding generic medication.[34] The role of pharmacists also is important within this debate. The success of the Hatch-Waxman act is in part attributable to the ability of pharmacists to substitute generic medications. The success of a follow-on biologic procedure likely will hinge on the ability of pharmacists to dispense approved follow-on products as well.

Recommendations for Future Pharmaceutical Policy for Biologics

It is of interest to consider the manner in which the biotechnology industry has been able to reap the benefits of pharmaceutical regulatory reform (i.e., by regaining patent life for time lost in regulatory review and clinical testing) without being required to make the concessions other brand-name manufacturers have had to (i.e., relaxed market entry for multi-source products). The implications of regulatory oversight without an abbreviated pathway are difficult to forecast. However, if we consider the history of generics for small molecule drugs, several observations can be made. First, it is economically inefficient to require duplicate testing for products when their safety and efficacy has already been established.[10] Second, a diminished threat of competition stifles the drive for continued innovation in the pharmaceutical industry. Finally, lack of an abbreviated process for generic producers severely limits generic market entry and competition in the pharmaceutical market and keeps drug prices artificially elevated.[15,16]

Some economists have argued that monopolistic practices for pharmaceuticals are inefficient creating a dead weight loss to society.[34] Dead weight loss is a measure of the degree to which consumer losses from higher prices are not offset by greater revenue to producers. Conservative estimates of dead weight loss in the U.S. pharmaceutical industry have placed the value between 3 and 5 billion dollars.[34,35] This inefficiency increases as producers capitalize on existing monopolies through rent seeking activities such as lobbying, litigation, and aggressive marketing.

Under ideal circumstances, the decrease in drug prices through generic competition would result in net gains to society through more affordable medications and increased availability of new and innovative drugs. For example, a study by the Congressional Budget Office estimated the net benefit of savings from generic substitution in 1994 at roughly $8 to $10 billion in retail spending for prescription drugs.[17] This has provided the impetus for allowing high prices of innovative prescription drugs in the short term with the understanding that after sufficient return on capital, product costs would decrease through generic availability. In doing so, access to existing drug therapies would improve through lower prices. In addition, previous evidence suggests that erosion of brand market share by generic competition does not limit the incentive for continued innovation by pioneering pharmaceutical firms.[36]

Given past experience, clear regulatory guidance for follow-on biologics is necessary. Regulatory change in the pharmaceutical industry typically has come from either its oversight agency (FDA) or U.S. congressional bodies. As mentioned previously, the FDA's opportunities to create a defensible case-by-case approach to the approval of follow-on biologics have been stalled by special interests. In addition, recent criticism of the FDA's handling of post-market surveillance for approved drug products and flu vaccine shortages have prioritized their primary

mission of safety.[37] Due to the current environment at FDA, it seems unlikely they will make a decision on how to handle follow-on biologics in the short-term. Even if the agency does come to a conclusion, it will be hotly contested by various stakeholders. Thus, it seems more likely that a final resolution will come from congress. Congress has been active on the issue, recently holding public hearings, but has not yet reached consensus on the best course of action.[23]

In light of current technological capabilities, a multi-tiered approach to approval of follow-on biologics could be successful.[38] We would argue that decision authority should be retained by the FDA and the review process should be given the flexibility to handle the uniqueness of each follow-on product. For example, the first tier in the review process could include comparative characterization through analytical testing of the follow-on biologic and a reference product using available technologies. The study results could then be evaluated by FDA to determine whether additional preclinical (tier two) or clinical (tier three) testing is required. We suggest that a precedent does exist with FDA to allow innovative firms to request product approval after changes in the manufacturing process. For example, during market approval of drotrecogin alfa (Xigris-Eli Lilly) for treatment of severe sepsis, the company made significant changes to the manufacturing process during clinical testing and the FDA approved the product based on tests of 'sameness'.[39,40]

In addition to a tiered review process, companies could be given the authority to challenge existing patents of sole-source biologics. This would be an important instrument to counteract life cycle management strategies utilized by originator companies. Life cycle management includes a variety of tactics intended to deter or delay market entry by generic competitors and extend the effective patent life of a branded biologic. 'Patent stacking' is one example of life cycle management. The process consists of staggered patent filings aimed at

extending the total patent life of a single-source product. Erythropoietin (Epogen-Amgen) is a prime example. The company's first patent for erythropoietin was granted in 1987 and its "last" patent does not expire until 2015.[41] If not contested, Amgen would receive nearly 30 years of patent protection on this biologic.

Finally, companies could be given the authority to begin testing and evaluating potential follow-on biologics before patent expiration of the sole-source product. Early development would permit competitors time to collect information and collaborate with FDA to ensure availability of safe and effective follow-on biologics. As the process develops, regular analysis of the consequences due to regulatory reform could be conducted to allow for policy refinement as needed. Establishment of an effective system for abbreviated approval of follow-on biologics will require substantial cooperation among all stakeholders. As such, we believe that political action will be a necessary and important step in the direction towards regulatory reform of biologics.

Conclusions

The subject of follow-on biologics has experienced considerable debate and will continue to do so as additional biologics approach patent expiration without a well defined regulatory policy. The potential for creation of a system allowing abbreviated approval for follow-on biologics exists and the need for action is becoming more urgent as multiple single-source biologics approach patent expiration. Other countries already are moving forward with biogeneric regulatory policy and are actively approving follow-on biologics.[42,43] We propose that creation of an abbreviated system in the U.S. should emphasize safety, while creating price competition and providing stimulus for continued innovation in the biologic market.

Disclaimer:

The views expressed in this paper are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the United States Government.

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Table 1: Sales History of Biopharmaceuticals in 2003 MedAdNews Top 200 Drugs

Trade Name (Generic Name)	Manufacturer	Condition	Original Approval	Sales in million US Dollars			
				2003	2002	2001	2000
Humulin (insulin)	Eli Lilly	Diabetes	10/28/1982	1060	1004	1061	1137
Intron A, Peg-Intron, & Rebetol (ribivarin/ interferon alfa)	Schering Plough	Cancer & viral infections	6/4/1986	1851	2736	1447	1360
Humatrope (somatropin)	Eli Lilly	Growth Failure	3/8/1987	371	329	313	303
Infanrix/ Pediarix (diptheria, tetanus, pertussis vaccine)	Glaxo-Smith-Kline	Diptheria, Tetanus, Pertussis Vacine	3/8/1987	551	381	343	259
Epogen (epoeitin alfa)	Amgen	Anemia	6/1/1989	2435	2261	2158	1960
Engerix-B, Havrix, & Twinrix (hepatitis vaccine)	Glaxo-Smith-Kline	Hepatitis A and B Vaccines	8/28/1989	684	725	641	700
Botox (botulinum toxin)	Allergan	Cervical dystonia	12/29/1989	564	440	310	240
Epogin (epoetin beta)	Chugai Pharm.	Anemia	4/1/1990	551	501	455	440
Procrit /Eprex (epoetin Alfa)	Johnson & Johnson	Anemia	12/31/1990	3984	4269	3430	2709
Neupogen (filgrastim)	Amgen	Neutropenia	1/20/1991	1267	1380	1300	1220
Cerezyme/ Ceredase (imiglucerase / alglucerase)	Genzyme	Gaucher Disease	4/5/1991	739	619	570	537
NovoSeven (eptacog alfa)	Novo Nordisk	Hemophilia	4/22/1992	589	459	372	280
Kogenate (octocog alfa)	Bayer	Hemophilia	2/25/1993	562	378	231	453
Betaseron (interferon beta 1b)	Schering AG	MS[1]	7/23/1993	871	740	610	547
Integrilin (eptifibatide)	Millenium/ Schering Plough	ACS[2]	5/17/1994	306	304	231	172
ReoPro (abciximab)	Eli Lilly	ACS[2]	12/22/1994	364	384	431	419
Genotropin (somatropin)	Pfizer	Growth failure	8/24/1995	481	551	511	467
Gonal-F (follitropin alfa)	Serono	Infertility	10/25/1995	526	450	411	366

Table 1 Continued: Sales History of Biopharmaceuticals

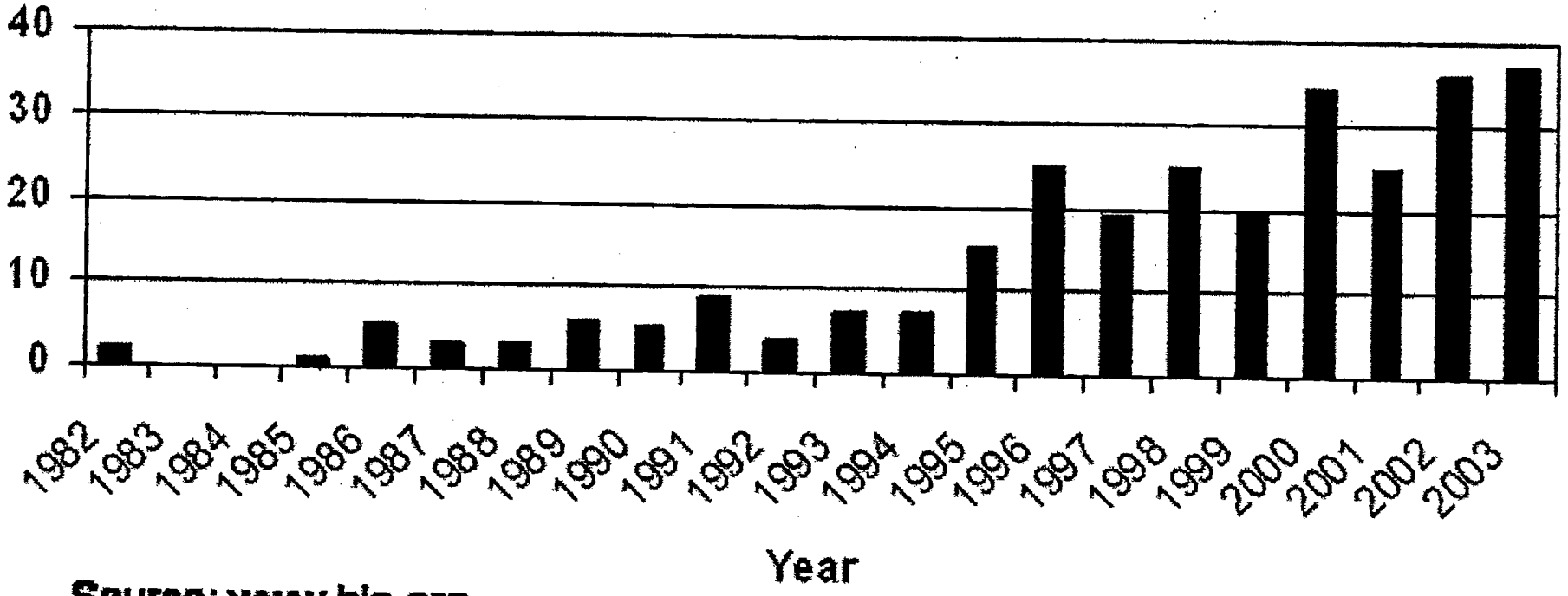
Humalog (insulin)	Eli Lilly	Diabetes	4/30/1996	1021	834	628	350
Follistim/ Puregon (follitropin beta)	Akzo Nobel	Infertility	5/3/1996	375	337	295	260
Avonex (interferon beta 1a)	Biogen Idec	MS[1]	5/17/1996	1168	1034	972	761
NeoRecormon (epoetin beta)	Roche	Anemia	7/16/1997	927	766	442	384
Rituxan/ MabThera (rituximab)	Genentech/ Roche	Non-Hodgkin Lymphoma	12/26/1997	2063	1530	1003	532
Rebif (interferon beta 1a)	Serono	MS[1]	2/1/1998	819	549	380	254
Synagis (palivizumab)	MedImmune	RSV[3]	6/19/1998	849	668	516	427
Remicade[4] (infliximab)	Johnson & Johnson / Schering Plough	Arthritis & Crohn's Disease	8/24/1998	2269	1634	887	427
Herceptin (trastuzumab)	Roche/ Genentech	Breast cancer	9/25/1998	875	646	477	320
Enbrel (etanercept)	Amgen	Arthritis	11/2/1998	1300	802	762	652
Prevnar (pneumococcal vaccine)	Wyeth	Pneumonia	2/17/2000	946	648	798	461
Visudyne (verteporfin)	Novartis	Macular degeneration	4/12/2000	357	286	224	98
Lantus (insulin)	Aventis	Diabetes	4/20/2000	551	299	132	n/a
Gleevec/Glivec (imatinib)	Novartis	Leukemia, cancer	5/10/2001	1128	615	153	n/a
Aranesp (darbepoetin alfa)	Amgen	Anemia	6/11/2001	1544	416	42	n/a
Pegasys/ Copegus (peginterferon alfa 2a / ribivarin)	Roche	Hepatitis-C	8/7/2001	700	n/a	n/a	n/a
Neulasta (pegfilgrastim)	Amgen	Neutropenia	1/31/2002	1255	464	n/a	n/a
			Sales per year	35903	29439	22536	18495

Source: MedAdNews

1 - Multiple Sclerosis, 2 - Acute Coronary Syndrome, 3 - Respiratory Synctial Virus

4 - Combines sales for both Schering Plough and Johnson & Johnson are reported

Figure 1: Number of New Biopharmaceutical Drug and Indication Approvals per year



Source: www.bio.org